CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215309Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 16, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 215309
Product Name and Strength:	Opzelura (ruxolitinib) cream, 1.5%
Applicant/Sponsor Name:	Incyte Corporation
OSE RCM #:	2020-2688-1
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on August 27, 2021 for Opzelura. Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Opzelura (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel, M. Label and Labeling Review for Opzelura (NDA 215309). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 30. RCM No.: 2020-2688.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
09/16/2021 09:24:32 AM

SEVAN H KOLEJIAN
09/16/2021 01:42:21 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	September 15, 2021
Reviewer:	Joel L. Wessfeld, MD MPH Division of Epidemiology I
Deputy Director:	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo
Drug Name(s):	ruxolitinib cream (OPZELURA)
Application Type/Number:	NDA 215309
Submission Number:	eCTD 0001
Applicant/sponsor:	Incyte Corporation
OSE RCM #:	2021-1039

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 215309 seeks FDA approval for OPZELURA™ (ruxolitinib cream) as a JAK kinase (JAK) inhibitor for the topical treatment of atopic dermatitis. OPZELURA™ (ruxolitinib cream) and JAKAFI™ (ruxolitinib tablet; NDA 202192) contain the same active ingredient (ruxolitinib phosphate, molecular weight 404.36), a selective inhibitor of JAK1 and JAK2 (intracellular mediators of cytokine signaling). FDA-approved treatment indications for JAKAFI™ include (1) myelofibrosis, (2) polycythemia vera, and (3) steroid-refractory acute graft-versus-host disease.

The OPZELURA™ label drafted by Incyte (1) recommends topical application "twice daily to affected areas up to 20% body surface area" and (2) shows a terminal pharmacokinetic half-life (after topical application) of (b) (4) hours.[a]

1.2. Describe the Safety Concern

Atopic dermatitis (a chronic inflammatory skin disease) occurs in children and adults, including women in reproductive age groups. JAK molecular pathways regulate cell adhesion and cell polarity, biologic processes important to embryonic development.[b] A maximal use pharmacokinetic study demonstrated potential for systemic absorption from topical application.[c] Taken together, these factors establish a potential for serious risk for adverse pregnancy, fetal, or infant outcomes from use of ruxolitinib cream during pregnancy.

APPENDIX 1 summarizes results from studies in pregnant animals.

- One study showed 9% lower fetal weights in pregnant rats treated with ruxolitinib at 22 times the maximum recommended human dose (MRHD).
- A second study showed 8% lower fetal weights in pregnant rabbits treated with ruxolitinib at 0.7 times MRHD.
- A third study in rats showed no adverse effects from ruxolitinib treatment at 3.1 times MRHD on embryofetal survival or postnatal growth.

For labeling purposes, clinical studies of ruxolitinib cream provide insufficient information about safety during pregnancy. The clinical safety database for ruxolitinib cream (as of April 30, 2021) contains nine instances of pregnancy exposure with outcomes described as (1) full-

[a] Prescribing Information for OPZELURA™ (ruxolitinib) cream, for topical use, submitted to NDA 215309 (eCTD 001) on December 21, 2020.

[b] Limpert JL, MC Dinatale, and LP Yao, Division of Pediatric and Maternal Health Review, OPZELURA (ruxolitinib) 1.5% cream, filed under NDA 215309 on May 24, 2021 (DARRTS Reference ID: 4799814), p 14.

[c] Limpert JL, *op. cit.*, p 14.

term birth without congenital malformation (n=2), (2) termination because of molar pregnancy (n=1), (3) spontaneous abortion (n=2), (4) induced abortion (n=1), and (5) outcome unknown (n=3).[d] The sponsor's pharmacovigilance database for oral ruxolitinib contains (as of February 22, 2021) 36 instances of pregnancy exposure with outcomes described as (1) livebirth (N=4) including one livebirth with a congenital malformation (ambiguous genitalia), (2) fetal death (n=1), (3) spontaneous abortion (n=4), (4) induced abortion (n=7), and (5) outcome unknown (n=20).[e]

Citing "anticipated use of ruxolitinib in females of reproductive potential who may become pregnant" in combination with "the limited information to date," the Division of Pediatric and Maternal Health (DPMH) recommended a pregnancy registry and a complementary study as separate Post-Marketing Requirements (PMRs).[f] DPMH presented the registry PMR as a means for assessing "major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to ruxolitinib during pregnancy."[g,h] Citing typically slow accrual to pregnancy registries, DPMH presented earlier availability of information as a rationale for a complementary study.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision

[d] Limpert, *op. cit.*, pp 5-6.

[e] Limpert, *op. cit.*, pp 6-9.

[f] Limpert, *op. cit.*, pp 14-15.

[g] Limpert, *op. cit.*, p 15.

[h] PMR scope clarified as "ruxolitinib cream for the atopic dermatitis population." Email communication from J Limpert to J Weissfeld on May 24, 2021, 3:47 PM.

and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☒ Electronic database study without chart review (*e.g.*, retrospective cohort study using claims or electronic medical record data)

☒ Other, please specify: additional pregnancy study using a different design (*e.g.*, case-control study in a pre-existing pregnancy or birth defect registry)

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population

☐ Exposures

☒ Outcomes (pregnancy registry)

☒ Covariates (pregnancy registry)

☒ Analytical Tools (additional pregnancy study)

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to medical records. A pregnancy registry entails collection of detailed patient information. A requirement for detailed patient information necessitates data collection not possible in the Sentinel Distributed Database (SDD). The patient information requirement covers both details about (1) drug and concomitant exposures (e.g., precise timing of specific exposures in relation to days before or after pregnancy onset) and (2) outcomes of interest (e.g., specific type of congenital malformation). Pregnancy registry requirements for accurate classification of congenital malformation outcomes necessitate independent review of primary source documents by physicians with special training or expertise in clinical genetics or birth defects.

Covariates: Unlike a pregnancy registry, SDD provides incomplete information about critical covariates (*e.g.*, smoking, folate supplementation, and family history of birth defects).

Analytical tools: The requested PMRs target more than one outcome, including major congenital malformations (MCM), spontaneous abortions, stillbirths, small for gestational age, and preterm birth. Moreover, the MCM outcome covers several subclasses of potential interest (e.g., congenital malformation of the circulatory system, congenital malformation of the nervous system, or cleft lip and cleft palate). ARIA might address the complexity presented by multiple discrete outcomes by means of an appropriate data mining approach. However, a suitable data

mining approach (e.g., TreeScan) is not yet available for signal detection of birth defects and other pregnancy outcomes in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

PMR #1: Conduct a Pregnancy Exposure Registry, a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes in the female atopic dermatitis population exposed to ruxolitinib cream during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. For more information, see the May 2019 FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies.

PMR #2: Conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in the female atopic dermatitis population exposed to ruxolitinib cream during pregnancy compared to an unexposed control population.

APPENDIX 1: Section 8.1 text recommended by DPMH for OPZELURA™ (ruxolitinib cream)

8.1 Pregnancy

Pregnancy Exposure Registry

There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling XXX-XXX-XXXX.

Risk Summary

Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity (see Data).

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data

Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD; the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% body surface area is used for calculation of multiples of human exposure). In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure.

In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOEL L WEISSFELD
09/15/2021 04:28:33 PM

SUKHMINDER K SANDHU
09/15/2021 04:33:25 PM

JUDITH W ZANDER
09/15/2021 04:58:25 PM

SARAH K DUTCHER
09/15/2021 09:42:41 PM

ROBERT BALL
09/16/2021 08:41:28 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 25, 2021
To:	Matthew White Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Laurie Bounaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication (MG)
Drug Name (established name):	OPZELURA (ruxolitinib)
Dosage Form and Route:	cream, for topical use
Application Type/Number:	NDA 215309
Applicant:	Incyte Corporation

1 INTRODUCTION

On December 21, 2020, Incyte Corporation submitted for the Agency's review a New Drug Application (NDA) 215309 for OPZELURA (ruxolitinib) cream, for topical use. OPZELURA (ruxolitinib cream) is proposed for the topical treatment of atopic dermatitis in patients 12 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on January 28, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OPZELURA (ruxolitinib) cream, for topical use.

2 MATERIAL REVIEWED

- Draft OPZELURA (ruxolitinib) cream, for topical use MG received on December 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 19, 2021.
- Draft OPZELURA (ruxolitinib) cream, for topical use Prescribing Information (PI) received on December 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 19, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN W REDWOOD
08/25/2021 10:15:44 AM

LAURIE J BUONACCORSI
08/25/2021 10:32:53 AM

SHAWNA L HUTCHINS
08/25/2021 10:36:10 AM

LASHAWN M GRIFFITHS
08/25/2021 12:27:18 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 25, 2021

To: Brenda Carr, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Snezana Trajkovic, MD, Clinical Team Leader, DDD
Matthew White, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments OPZELURA™ (ruxolitinib) cream, for topical use.

NDA: 215309

In response to DDD's consult request dated August 20, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for OPZELURA™ (ruxolitinib) cream, for topical use (Opzelura).

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on August 19, 2021, and our comments are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by the electronic document room on April 1, 2021, and we have no comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURIE J BUONACCORSI
08/25/2021 10:29:31 AM

Choose an item.**Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 9, 2021
To:	Matthew White Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Bounaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	OPZELURA (ruxolitinib)
Dosage Form and Route:	cream, for topical use
Application Type/Number:	NDA 215309
Applicant:	Incyte Corporation

1 INTRODUCTION

On December 21, 2020, Incyte Corporation submitted for the Agency's review a New Drug Application (NDA) 215309 for OPZELURA (ruxolitinib) cream, for topical use. OPZELURA (ruxolitinib cream) is proposed for the topical treatment of atopic dermatitis in patients 12 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on January 28, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for OPZELURA (ruxolitinib) cream, for topical use.

2 MATERIAL REVIEWED

- Draft OPZELURA (ruxolitinib) cream, for topical use PPI received on December 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 28, 2021.
- Draft OPZELURA (ruxolitinib) cream, for topical use Prescribing Information (PI) received on December 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 28, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN W REDWOOD
06/09/2021 10:23:39 AM

LAURIE J BUONACCORSI
06/09/2021 10:32:18 AM

LASHAWN M GRIFFITHS
06/09/2021 11:16:37 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 3, 2021

To: Brenda Carr, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Snezana Trajkovic, MD, Clinical Team Leader, DDD
Matthew White, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments OPZELURA™ (ruxolitinib) cream, for topical use.

NDA: 215309

In response to DDD's consult request dated January 28, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for OPZELURA™ (ruxolitinib) cream, for topical use (Opzelura).

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on May 28, 2021, and our comments are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DDD on May 28, 2021, and we have no comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURIE J BUONACCORSI
06/03/2021 01:06:01 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: May 21, 2021 **Date consulted:** May 3, 2021

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dentistry (DDD)

Drug: OPZELURA (ruxolitinib) 1.5% cream

NDA: 215309

Applicant: Incyte Corporation

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For the topical treatment of atopic dermatitis in patients 12 years of age and older

Materials Reviewed:

- DPMH consult request dated May 3, 2021, DARRTS reference ID 4789552
- Applicant's submitted background package and proposed labeling for NDA 215309
- Applicant's May 17, 2021 response to the Information Request for NDA 215309

- DPMH labeling review for Rinvoq (upadacitinib), NDA 211675, April 27, 2021, Christos Mastroyannis, MD, Medical Officer, MD, Medical Officer, DARRTs reference ID: 4786528[1]
- DPMH review for Cibinqo (abrocitinib), NDA 213871, by Jean Limpert, MD, Medical Officer, dated February 16, 2021, DARRTS Reference ID: 4715000.[2]
- DPMH review for Olumiant (baricitinib), NDA 207924, by Jean Limpert, MD, Medical Officer dated February 8, 2021, DARRTS Reference ID: 4742935.[3]
- DPMH addendum review for Olumiant (baricitinib), NDA 207924, by Jean Limpert, MD, Medical Officer dated March 23, 2021, DARRTS Reference ID: 4768173.[4]

Consult Question: "PLLR labeling review"

INTRODUCTION AND BACKGROUND

On December 21, 2020, Incyte Corporation submitted a new drug application (NDA) for Ruxolitinib cream via the 505(b)(1) pathway. On May 3, 2021, DDD consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Ruxolitinib cream is not currently approved in any country. The proposed indication is for the topical treatment of atopic dermatitis in subjects 12 years of age and older. The applicant is also evaluating ruxolitinib cream for other inflammatory skin conditions including psoriasis, vitiligo, and alopecia areata.
- Ruxolitinib phosphate drug substance used in ruxolitinib cream is also the active component of Jakafi (ruxolitinib) tablet (NDA 202,192) which received initial approval in 2011. The approved indications for oral ruxolitinib are the treatment of intermediate myelofibrosis, polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea, and steroid refractory acute graft-versus-host disease in adult and pediatric patients 12 years and older.
- The JAK pathway is involved in cell adhesion and cell polarity which can affect early embryonic development. Animal data for the class of JAK inhibitors demonstrates varying degrees of embryofetal toxicity. There are currently no oral or topical JAK inhibitors approved for the treatment of atopic dermatitis. There are multiple oral JAK inhibitors currently under review by DDD for moderate-severe atopic dermatitis. DPMH is involved in these ongoing reviews. There are three JAK inhibitors approved for rheumatologic disease (i.e., tofacitinib, baricitinib, upadacitinib) which suggest varying levels of embryofetal toxicity in the embryofetal development studies and this range of severity is reflected in labeling. In current approved labeling, upadacitinib has an embryofetal warning with pregnancy testing and contraception recommendations, tofacitinib has a fetal harm statement in subsection 8.1 with contraception

[1] The Rinvoq review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[2] The Cibinqo review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[3] The Olumiant review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[4] The Olumiant review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

recommendations, and baricitinib includes a fetal harm statement in subsection 8.1 without contraception recommendations. For additional information about the DDD Pharmacology/Toxicology and DPMH discussion about JAK inhibitors and embryofetal toxicity the reader is referred to the DPMH review for baricitinib.[5]

- On May 10, 2021, the Agency requested information to support the Pregnancy and Lactation Labeling section for this product. On May 17, 2021, the applicant responded to the IR.

Drug Characteristics[6]

- Drug class: Janus kinase (JAK) inhibitor
- Mechanism of Action: Ruxolitinib is a Janus Kinase (JAK) inhibitor and inhibits JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.
- Dosage and administration: Apply a thin layer twice daily to affected areas of up to 20% of body surface area.
- Molecular weight: 404.4 Daltons
- Absorption: Plasma concentrations of ruxolitinib were quantifiable in all subjects. In adult subjects, the mean ± SD maximum plasma concentration (C_{max}) and area under the concentration time curve from 0 to 12 hours post dose (AUC_{0-12}) for ruxolitinib on Day 1 were 449 ± 883 nM and 3215 ± 6184 h*nM, respectively.
- Half-life: (b) (4) hours (mean terminal half-life following topical application)
- Protein binding: 97%
- Serious adverse reactions: thrombocytopenia, anemia, neutropenia, infection, progressive multifocal leukoencephalopathy, herpes zoster, non-melanoma skin cancer, lipid elevations

REVIEW

PREGNANCY

Atopic Dermatitis and Pregnancy

It is estimated up to 10% of adults in the United States are affected by AD though prevalence estimates are limited and vary because AD is a clinical diagnosis.[7] Approximately half of the AD population are females, and AD affects all age groups including females of reproductive potential.[8] In about half of cases, AD may worsen during pregnancy and untreated AD may put a pregnant person at risk for infections (e.g., eczema herpeticum, *Staphylococcus aureus*

[5] DPMH addendum review for Olumiant (baricitinib), NDA 207924, by Jean Limpert, MD, Medical Officer dated March 23, 2021, DARRTS Reference ID: 4768173.

[6] OPZELURA (ruxolitinib) proposed labeling

[7] Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: a cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population. *J Invest Dermatol.* 2019;139(3):583-590.

[8] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* **10,** 1215–1228 (2020).

infections).[9] Some atopic diseases are associated with decreased fertility, but the relationship for AD and reduced fertility is less clear.[10,11]

Initial therapies include topical treatments and phototherapy. Currently approved topical therapies include topical corticosteroids, topical calcineurin inhibitors (e.g., tacrolimus ointment, pimecrolimus cream), and topical phosphodiesterase 4 inhibitor (e.g., crisaborole). Topical corticosteroids with low potency are typically first-line treatment for AD during pregnancy.

Systemic therapies are recommended when AD is not adequately controlled by these initial therapies. There are currently two approved systemic therapies for patients with moderate-severe AD (i.e., systemic corticosteroids and dupilumab). Systemic corticosteroids can be effective for severe acute exacerbations but are not recommended for long-term use. Dupilumab is an injectable systemic IgG4 monoclonal antibody that binds to the IL-4 Rα subunit and inhibits IL-4 and IL-13. Current data in pregnancy are limited to one case report and limited cases in clinical trials, but there are no known safety issues for use during pregnancy. [12,13,14]

Nonclinical Experience

Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose.

In rats, decreased fetal weight was noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD). The clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% body surface area was used for calculation of multiples of human exposure. The no adverse observed effect level (NOAEL) for both maternal toxicity and embryofetal toxicity was identified at 30 mg/kg/day (3.5 times the MRHD).

In rabbits, lower fetal weights and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day (0.7 times the MRHD). The NOAEL for embryofetal toxicity and maternal toxicity was 0.1 times the MRHD.

In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day (3.1 times the MRHD clinical

[9] Napolitano M, Ruggiero A, Fontanella G, Fabbrocini G, Patruno C. New emergent therapies for atopic dermatitis: A review of safety profile with respect to female fertility, pregnancy, and breastfeeding. Dermatol Ther. 2021 Jan;34(1):e14475.
[10] Langan, S.M.; Irvine, A.D.; Weidinger, S. Atopic dermatitis. Lancet 2020, 396, 345–360.
[11] Napolitano M, Ruggiero A, Fontanella G, Fabbrocini G, Patruno C. New emergent therapies for atopic dermatitis: A review of safety profile with respect to female fertility, pregnancy, and breastfeeding. Dermatol Ther. 2021 Jan;34(1):e14475.
[12] Kage P, Simon JC, Treudler R. A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. J Eur Acad Dermatol Venereol. 2020:34(6):e256–7.
[13] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* **10,** 1215–1228 (2020).
[14] DPMH labeling review for Dupixent, BLA 761055, January 13, 2017, Christos Mastroyannis, MD, Medical Officer, DARRTs reference ID: 4041992

systemic exposure). There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

For full details, the reader is referred to the Pharmacology/Toxicology review by Jiangyong Wang, PhD, which is currently pending.

Review of Pharmacovigilance Database

Topical Ruxolitinib

The clinical development program was comprised of 15 studies: 5 studies in participants with atopic dermatitis, 5 studies in patients with other inflammatory skin conditions, and 5 studies in healthy participants. The clinical program for atopic dermatitis consisted of ten studies using Ruxolitinib 1.5% cream. Pregnant persons were excluded from all clinical studies and females of reproductive potential were required to use effective contraception. As of April 30, 2021, there were a total of 13 cases of exposure to ruxolitinib cream during pregnancy. There were four pregnancies following paternal exposure and nine pregnancies following maternal exposure to topical ruxolitinib. Since there are no concerns for genotoxicity, the paternal exposures will not be described further. Outcomes were known for six pregnancies involving maternal exposure. No congenital anomalies were described. These cases are summarized in Table 1.

Table 1: Cases (n=6) with Known Pregnancy Outcomes for Maternal Exposure to Ruxolitinib Cream

Case Number/ Study ID[a] (Subject ID)	**Pregnancy Outcome**	**Length of Ruxolitinib Exposure During Pregnancy**	**Gestational Age At Birth/ Termination**	**Adverse Infant Outcome (for Live Births)**	**Perinatal Risk Factors**
(b) (6) INCB 18424-304 (b) (6)) (additional details provided below)	Abortion/ termination of molar pregnancy	Not provided	N/A	N/A	17-year-old; concurrent Chlamydial infection
(b) (6) INCB 18424-206 (b) (6))	Spontaneous abortion	5 weeks (estimate)	7 weeks (estimate)	N/A	Borderline hypertension, history of preeclampsia
(b) (6) INCB 18424-304 (b) (6)	Miscarriage	Off treatment (stopped therapy 1 day prior to last menstrual period)	Approximately 6.5 weeks	N/A	History of 7 miscarriages at 7 weeks' gestation
(b) (6) INCB 18424-204 (b) (6)	Abortion induced	Not provided	Not provided	N/A	Alcohol use
(b) (4) INCB 18424-202 (b) (6)	Live birth/healthy infant	Unknown	Full term	None	None

[redacted] INCB 18424-203 [redacted]	Live birth	2 weeks	39 weeks	None	Endometriosis

Reference: Applicant's table from May 17, 2021 IR response, modified by reviewer to reflect only cases of maternal exposure

Reviewer comment:
Two cases reported induced abortions. In one of the cases [redacted], a molar pregnancy was reported in a 17-year-old female. Young age is a risk factor for molar pregnancy. In both cases, key relevant details were not provided (e.g., timing and duration of ruxolitinib exposure, maternal history, concomitant medications). Two cases of spontaneous abortions were reported. In one case [redacted], the mother stopped ruxolitinib prior to her last menstrual period and had a history of multiple miscarriages, which is a risk factor for another spontaneous abortion. In the other case [redacted]), the mother was exposed to topical ruxolitinib for five weeks and had a spontaneous abortion at 7 weeks. The role of ruxolitinib cannot be excluded based on the timing of exposure. Two outcomes included healthy, full-term infants. A limitation is the timing and length of exposure is unknown for one pregnancy [redacted]) and reported as two weeks for the other pregnancy [redacted]). Overall, there are no obvious safety signals based on the limited data for these cases but no conclusions can be drawn regarding the safety of ruxolitinib during pregnancy.

Oral ruxolitinib
As of February 22, 2021, the applicant identified 54 cases following oral ruxolitinib exposure during pregnancy. There were 18 pregnancies following paternal exposure and 36 pregnancies following maternal exposure. Since there are no concerns for genotoxicity, the paternal exposures will not be described further. Of the 36 pregnancies 20 had unknown outcomes. Case details from the 16 pregnancies with known outcomes are summarized in Table 2.

Table 2: Case details for Known Pregnancy Outcomes for Maternal Exposure to Oral Ruxolitinib (n=16)

Case Number/Study ID	Pregnancy Outcome	Estimated Length Of Ruxolitinib Exposure During Pregnancy	Gestational Age At Birth/Termination	Adverse Infant Outcome (For Live Births)	Perinatal Risk Factors
(b) (6) (b) (6)	Spontaneous abortion	Not provided	Not provided	N/A	History of smoking, Polycythemia Vera, recent UTI, possible fetal exposure to aspirin, hydroxyurea and Zoloft
(b) (6) Spontaneous	Missed abortion	Exposed within first trimester	Not provided	N/A	Not provided
(b) (6) Spontaneous	Abortion	Not provided	Not provided	N/A	Not provided
(b) (6) Spontaneous	Abortion	Exposed within first trimester	3 months	N/A	Not provided
(b) (6) Literature	Abortion induced	Not provided	Not provided	N/A	Not provided
(b) (6) (b) (6)	Abortion induced	Not provided	Not provided	N/A	Not provided
(b) (6) (b) (6)	Abortion induced	Approximately 12 weeks	Approximately 12 weeks	N/A	Not provided
(b) (6) (b) (6)	Abortion induced	Exposed within first trimester	Not provided	N/A	Not provided
(b) (6) (b) (6)	Abortion induced	Not provided	Not provided	N/A	Not provided
(b) (6) (b) (6)	Abortion induced	Not provided	7 weeks	N/A	Not provided

(b) (6) Spontaneous	Abortion induced	Not provided	Not provided	N/A	Not provided
(b) (6)	Fetal demise/fetal death	Exposed within first trimester	Not provided	N/A	Not provided
(b) (6) Spontaneous	Live birth	Approximately 10 weeks	Not provided	Not provided	Not provided
(b) (6) Patient Oriented	Live birth	Not provided	Not provided	Not provided	Not provided
(b) (6) Spontaneous	Live birth/normal baby	Not provided	Not provided	None	Tobacco user
(b) (6)	Congenital anomaly	12 weeks (+/-4)	35 weeks	Ambiguous genitalia	Not provided

` Reference: Applicant's table from May 17, 2021 IR response, modified by reviewer to reflect only cases of maternal exposure

Reviewer comment:
Eleven cases had an outcome of abortion and of these, seven were induced abortions. Fetal abnormalities were not reported but the reasons for induced abortions were not provided. In one case of abortion, the mother had risk factors including smoking. In general, information needed to make a causal assessment were missing, including timing and length of ruxolitinib exposure, maternal history, and concomitant medications.

There was also one fetal death (unknown gestational age; (b) (6) *following exposure to oral ruxolitinib in the first trimester. Relevant details, including the timing of the fetal death, length of ruxolitinib exposure in the first trimester, and maternal history were missing. It is also possible that adverse pregnancy outcomes for oral ruxolitinib may be due to underlying maternal disease, although the condition for the drug was prescribed was not specified.*

The applicant provided the following information for the case involving a congenital anomaly.

Case Number	Congenital Anomaly	Case Summary
(b) (6)	Ambiguous genitalia	A male neonate born to a 27-year-old female patient, who was treated with oxymetholone and ruxolitinib for myeloproliferative neoplasm (MPN), was found to have ambiguous genitalia 1 week after birth. Neonate's mother had initially received oxymetholone for MPN and discontinued after 5 months. Four months after oxymetholone discontinuation, she started ruxolitinib therapy for MPN with last menstrual period 5 days before. Eleven weeks after starting ruxolitinib therapy, ultrasound revealed a single live fetus of 12 +/- 4 weeks. Ruxolitinib was stopped due to pregnancy. Four weeks later, neonate's mother again started receiving oxymetholone. The mother had cesarean delivery at 35 weeks and delivered a male baby weighing 2 kg with height 42cm, Apgar scores 8/10 and head circumference 30 cm. Neonate was alive with no congenital abnormality noted at the time of birth. After 1 week of birth, the neonate was noted to have ambiguous genitalia. Treatment with oxymetholone was discontinued and she was started on ruxolitinib. The linked mother case is databased as (b) (6)
Comment: *A causal relationship between ruxolitinib exposure and ambiguous genitalia in a neonate born to a female patient is considered unlikely. Considering the known virilizing potential of oxymetholone, late detection of the malformation and unknown karyotype of the neonate, the observed malformation may be attributed to the fetal exposure to this drug. Oxymetholone, a 17alpha-alkylated anabolic/androgenic steroid used for the treatment of anemias caused by deficient red cell production, is contraindicated in women who are or may become pregnant. Non-clinical studies revealed its virilizing activities in female rat fetuses* (Kawashima et al 1977).		

Reviewer comment: The case of the premature infant with a congenital anomaly (ambiguous genitalia) appears to be unlikely related to ruxolitinib. This reviewer agrees that exposure to oxymetholone, a drug contraindicated in pregnancy with known androgenic effects, including virilization of genitalia, is likely related to the ambiguous genitalia in the neonate.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in Embase and Ovid for literature related to ruxolitinib and pregnancy. The applicant's search strategy is provided in the May 17, 2021 IR response. The applicant provided a summary table of seven articles. See Appendix B for details. The applicant states the articles did not reveal new or significant safety information.

DPMH Review of Literature
DPMH performed a search in PubMed, Embase, Micromedex, [15] TERIS, [16] Reprotox, [17] and Briggs[18] to find relevant articles related to the use of ruxolitinib during pregnancy Search terms included "ruxolitinib" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," "miscarriage," and "fetal loss." No publications were identified.

Reprotox states, "ruxolitinib did not increase malformations in experimental animals. We did not locate human data."

The Micromedex pregnancy rating for oral ruxolitinib is "fetal risk cannot be ruled out. Available evidence is inconclusive or is inadequate for determining fetal risk when used in pregnant women or women of childbearing potential. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during pregnancy."

TERIS did not identify data and determine the teratogenic risk as "undetermined." TERIS states, "although the teratogenic risk of this agent is undetermined, it may be substantial because ruxolitinib inhibits signaling molecules involved in embryonic development."

Briggs (2015) pregnancy recommendation for ruxolitinib is "contraindicated." The authors state, "no reports describing the use of ruxolitinib in human pregnancy have been located. The animal data suggested risk (reduced fetal weights and late resorptions in two species) but these effects occurred with doses that were maternally toxic. However, lower nonmaternal toxic doses in rats were associated with post implantation losses. Although the drug's mechanism of action suggests that use in pregnancy could cause fetal harm, the absence of human pregnancy experience prevents a better assessment of the embryo-fetal risk. If the drug is indicated in a pregnant woman, she should be informed of the potential risk to her embryo-fetus."

LACTATION
Nonclinical Experience
Lactating rats were administered a single dose of [C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

For full details, the reader is referred to the Pharmacology/Toxicology review by Jiangyong Wang, PhD, which is currently pending.

[15] https://www.micromedexsolutions.com, accessed 5/7/21
[16] Truven Health Analytics information. Teris, accessed 5/11/21
[17] Truven Health Analytics information. Reprotox, accessed 5/11/21
[18] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 5/11/21

Review of Pharmacovigilance Database

As of April 30, 2021, the applicant did not identify any cases pertaining to lactation for ruxolitinib cream in the global safety database.

For oral ruxolitinib, the applicant identified three cases reported as "mastitis." One described a breast infection in a 48-year-old female following bilateral mastectomy. One case described idiopathic granulomatous mastitis in a 67-year-old male and the last case described a recurrent breast fungus in an adult female patient. Therefore, no cases pertaining to lactation were identified for oral ruxolitinib.

Reviewer comment: This reviewer agrees that the cases of mastitis do not appear to be related to lactation.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in Embase and Ovid for literature related to ruxolitinib and lactation. The applicant's search strategy is provided in the May 17, 2021 IR response. The applicant did not identify any publications.

DPMH review of literature

This Reviewer performed a search in PubMed, Embase, Micromedex,[19] TERIS, [20] Reprotox, [21] and Briggs, [22] *Medications and Mothers' Milk* (not referenced),[23] and LactMed[24] to find relevant articles related to the use of ruxolitinib during lactation. Search terms included "ruxolitinib" AND "breastfeeding" or "lactation." No publications were identified.

The LactMed summary of use during lactation states, "no information is available on the clinical use of ruxolitinib during breastfeeding. Because ruxolitinib is 97% bound to plasma proteins, the amount in milk is likely to be low." LactMed did not identify information with respect to drug levels, effects in breastfed infants, or effects on lactation and breastmilk.

Briggs (2015) lactation recommendation is "contraindicated." The breastfeeding summary for oral ruxolitinib states, "No reports describing the use of ruxolitinib during human lactation have been located. The molecular weight of the parent drug (about 404) suggests that the drug, and possibly its two active metabolites, will be excreted into breast milk, but the high (97%) plasma protein binding and relatively short mean elimination half-lives (3 hours for the parent drug and 5.8 hours for the parent drug plus active metabolites) should limit the amount excreted. The effect of any exposure on a nursing infant is unknown. However, thrombocytopenia and anemia occurred in >20% of patients treated with the drug and >10% experienced bruising, dizziness, and headache. Thus, if the drug is given during breastfeeding, a nursing infant should be monitored for these adverse effects."

[19] https://www.micromedexsolutions.com, accessed 5/7/21
[20] Truven Health Analytics information. Teris, accessed 5/11/21
[21] Truven Health Analytics information. Reprotox, accessed 5/11/21
[22] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 5/11/21
[23] https://www.halesmeds.com, accessed 5/11/21
[24] https://www.ncbi.nlm.nih.gov/books/NBK501922/, 5/11/21

Micromedex lactation rating is "infant risk cannot be ruled out. Available evidence and/or expert consensus is inconclusive or inadequate for determining infant risk when used during breastfeeding. Weight the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding."

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Ruxolitinib was not found to be carcinogenic in the 6-month Tg.rasH2 transgenic mouse model or the 2-year oral rat carcinogenicity study. In a 2-year dermal mouse carcinogenicity study, no drug-related tumors were observed at topical doses of ruxolitinib cream up to 1.5% applied at 100 µl/day (2.8 times the MRHD clinical systemic exposure). Ruxolitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in an in vitro chromosomal aberration assay (cultured human peripheral blood lymphocytes) or an in vivo rat bone marrow micronucleus assay.

In a fertility study, ruxolitinib was administered orally to male rats prior to and throughout mating and to female rats prior to mating and up to the implantation day (gestation day 7). Ruxolitinib had no effect on fertility or reproductive function in male or female rats at doses up to 60 mg/kg/day (22 times the MRHD clinical systemic exposure). However, in female rats, doses of greater than or equal to 30 mg/kg/day (3.5 times the MRHD clinical systemic exposure) resulted in increased post-implantation loss.

For full details, the reader is referred to the Pharmacology/Toxicology review by Jiangyong Wang, PhD, which is currently pending.

Review of Pharmacovigilance Database

As of April 30, 2021, the applicant did not identify any cases pertaining to fertility for ruxolitinib cream in the global safety database.

For oral ruxolitinib, the applicant identified 12 cases related to fertility, four of which were deemed not relevant. Four cases reported non-serious events of hypogonadism, polycystic ovaries, varicocele, and haematospermia. The applicant reported there were limited details which precluded a proper medical assessment. The applicant also described one cases of estrogen deficiency in a female with a history of total hysterectomy who was on hormonal treatment with estradiol prior to therapy with ruxolitinib.

The applicant provided detailed information for the remaining three cases.[25]
Briefly, the cases include:

- 30-year-old female who received oral ruxolitinib (20 mg twice daily) for the treatment of primary myelofibrosis. She developed dysfunctional uterine bleeding, anemia, and thrombocytopenia. She required a blood transfusion and hospitalization.

  Applicant's assessment: Anemia and thrombocytopenia are expected events in the USPI for oral ruxolitinib and may have played a contributing role in the dysfunctional uterine bleeding. No information was provided if the patient intended to be pregnant and if

[25] Applicant's May 17, 2021 response to IR

fertility was ultimately affected.

Reviewer comment: Agree with applicant's assessment

- 55-year-old male patient with hypertension and myelofibrosis took oral ruxolitinib (40 mg daily). The patient developed grade 4 prostate adenocarcinoma. The patient was hospitalized for severe acute prostatitis due to E coli two days status post transrectal prostate biopsy. The patient was hospitalized for severe septic shock. Approximately six weeks after discharge, the patient's prostatic MRI showed prostate cancer and atrophy of the left seminal vesicle. The outcome and causality of the seminal vesicle atrophy was not reported.

  Applicant's assessment: The patient's family history and advanced age are significant risk factors for prostate cancer.

  Reviewer comment: The seminal atrophy was diagnosed on imaging and is of unclear clinical significance.

- 67-year-old male who received oral ruxolitinib (10 mg daily) from (b) (6) for the treatment of myelofibrosis. In (b) (6), he developed a testicular infection requiring hospitalization. The patient reported his "testicles burst" for which the outcome is unknown.

  Applicant's assessment: This case is not medically confirmed, however, the event of "testicles burst" was likely related to the underlying testicular infection.

  Reviewer comment: Agree with applicant's assessment. Additionally, the testicular event and possible rupture occurred several months after ruxolitinib treatment was stopped.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in Embase and Ovid for literature related to ruxolitinib and fertility. The applicant's search strategy is provided in the May 17, 2021 IR response. The applicant did not identify any publications.

DPMH review of literature

This Reviewer performed a search in PubMed, Embase, Reprotox[21] to find relevant articles related to the use of ruxolitinib and effects on fertility. Search terms included "ruxolitinib" AND "fertility," "infertility," "contraception," and "oral contraceptives." No publications were identified.

DISCUSSION AND CONCLUSIONS

Pregnancy

AD is a common disease that affects up to 10% of adults, including females of reproductive potential, and for which topical therapies may be needed. Based on discussion with the Clinical Pharmacology Team, the Clinical Pharmacology reviewer noted that pharmacokinetic studies

indicate that topical administration ruxolitinib cream is systemically absorbed, but the amount of systemic absorption for topical ruxolitinib depends on several factors including the amount of affected body surface area and severity of skin lesions. In the maximal use pharmacokinetic study, the mean ± SD maximum plasma concentration (C_{max}) and area under the concentration time curve from 0 to 12 hours post dose (AUC_{0-12}) for ruxolitinib on Day 1 were 449 ± 883 nM and 3215 ± 6184 h*nM, respectively. However, in a patient with severe atopic dermatitis involving a body surface area of 90% and using topical ruxolitinib, the Cmax and AUC were as high as 3820 and 26,600, respectively. For oral ruxolitinib, the mean Cmax and AUC increase proportionately over a single dose range of 5 mg to 200 mg. Mean ruxolitinib Cmax ranged from 205 nM to 7100 nM and AUC ranged from 862 nM*hr to 30700 nM*hr over a single dose range of 5 mg to 200 mg.[26] Therefore, in a patient with severe atopic dermatitis, topical ruxolitinib may result in significant systemic absorption.

The JAK pathway is involved in cell adhesion and cell polarity which can affect early embryonic development. Animal data for the class of JAK inhibitors demonstrates varying degrees of embryofetal toxicity. Adverse outcomes occurred in the context of maternal toxicity at 22 times the MRHD (rats) and 0.7 times the MRHD (rabbits). The NOAEL for both maternal toxicity and embryofetal toxicity was 3.5 times the MRHD and 0.1 the MRHD in rats and rabbits, respectively.

There are currently no published data regarding the safety of ruxolitinib use in pregnant persons. In clinical trials, pregnant persons were excluded, and females of reproductive potential were expected to use effective contraception. The applicant provided pharmacovigilance data which included 45 cases of maternal exposure to either topical or oral ruxolitinib and of these, half had unknown outcomes. For topical ruxolitinib, there were six known outcomes including two healthy infants, two induced abortions (one for a molar pregnancy), and two spontaneous abortions (one case with a history of prior miscarriages). For oral ruxolitinib, there were 16 cases of maternal exposure with known outcomes. One congenital anomaly of ambiguous genitalia was identified which had a plausible alternative explanation of a concomitant medication known to cause virilization. There were eleven abortions reported and of these, seven were induced abortions (fetal abnormalities not described) and it is possible these would have continued as normal pregnancies. In the other four cases of abortions, minimal details are provided and the role of oral ruxolitinib cannot be excluded. It is also possible that adverse pregnancy outcomes for oral ruxolitinib may be due to underlying maternal disease for which the drug is indicated (e.g., intermediate or high-risk myelofibrosis, polycythemia vera, steroid-refractory acute graft-versus-host-disease) and this subset of patients would generally be at higher risk than patients with atopic dermatitis who would receive topical ruxolitinib. In addition, the background risk of miscarriage is 15-20% of all pregnancies. The JAK pathway is involved in cell adhesion and cell polarity which may affect early embryonic development. Thus, while mechanistically possible that ruxolitinib would affect early embryonic development in pregnancy, the number of cases are too low and with too few details to assess if ruxolitinib increases the risk of adverse fetal outcomes.

Given the anticipated use of ruxolitinib in females of reproductive potential who may become

[26] Currently approved Jakafi (ruxolitinib) tablets labeling. Drugs@FDA. Accessed 5/20/2021.

pregnant, and the limited information to date, DPMH recommends PMRs for a pregnancy registry and complementary study. A pregnancy registry would assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to ruxolitinib during pregnancy. Although the pregnancy registry will be an important tool for the collection of safety data in pregnant women exposed to ruxolitinib, we anticipate it will take several years for a pregnancy registry to provide adequate information. Therefore, a complementary study may provide additional understanding regarding safety in pregnancy and may additionally address limitations inherent to a pregnancy registry providing greater confidence in the pregnancy outcomes that are observed. For more information, the reader is referred to the May 2019 FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies.[27] In addition, upon approval, DPMH recommends adding contact information regarding the pregnancy registry to labeling in Subsection 8.1.

Lactation

There are no available clinical data regarding the presence of ruxolitinib in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Ruxolitinib is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Since topical ruxolitinib has significant systemic absorption, there is a risk that topical use of ruxolitinib could lead to breastmilk accumulation. Due to the potential risks of serious adverse reactions in adult patients taking ruxolitinib (e.g., serious infections, thrombocytopenia, anemia, neutropenia), DPMH does not recommend breastfeeding during treatment and for at least one week (5 times the terminal half-life of (b) (4) hours) after the last dose of ruxolitinib.[28]

Given that ruxolitinib will be used in females of reproductive potential with atopic dermatitis and based on the lack of available data in lactating women, DPMH recommends a PMR for a clinical lactation (milk only) study to better understand whether the amount of drug present in human milk is clinically significant. Since DPMH does not recommend breastfeeding while taking ruxolitinib due to the risk of serious adverse findings in adults, DPMH recommends a milk only study that enrolls breastfeeding women prescribed ruxolitinib who are willing to discontinue breastfeeding. While enrollment of healthy lactating women for a milk only study is also possible, this population may not be ideal for topical administration since absorption decreases in healthy skin. If there is undetectable or minimal transfer, such a finding could potentially allow for breastfeeding in women who are taking ruxolitinib. For more information, see the May 2019 FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design.[29]

Females and Males of Reproductive Potential

Nonclinical data do not suggest ruxolitinib impacts fertility. The applicant identified a few cases of oral ruxolitinib in the pharmacovigilance database (none for topical ruxolitinib) but the cases do not suggest ruxolitinib adversely impacts fertility.

[27] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safetystudies-guidance-industry

[28] DPMH discussed with the interval time period with the Clinical Pharmacology team

[29] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design

The nonclinical data does not suggest embryofetal toxicity and the low number of pregnancies reported in clinical studies do not suggest an obvious safety issue. Thus, pregnancy testing and contraception recommendations are not needed at this time and subsection 8.3 will be omitted.

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on May 21, 2021. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry
There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling XXX-XXX-XXXX.

Risk Summary
Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity *(see Data)*.

The (b) (4) background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriages are 2-4% and 15-20% (b) (4), respectively.

Data
Animal Data
Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD; the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% body surface area is used for calculation of multiples of human exposure). In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day.

This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure.

In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

8.2 Lactation

Risk Summary

There are no data on the presence of ruxolitinib in human milk, the effects on the breast-fed (b) (4) or the effects on milk production. Ruxolitinib was present in the milk of lactating rats (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA during treatment and for (b) (4) after the last dose (approximately 5 elimination half-lives).

Data

Lactating rats were administered a single dose of [^{14}C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Inform patients to report their pregnancy to Incyte Corporation at XXX-XXX-XXXX [*see Use in Specific Populations (8.1)]*.

Lactation

Advise a patient not to breastfeed during treatment with OPZELURA and for (b) (4) after the last dose *[see Use in Specific Populations (8.2)]*.

DPMH RECOMMENDATIONS FOR POSTMARKETING REQUIREMENTS (PMR)

DPMH recommends the following:

1. The applicant should be required to conduct a Pregnancy Exposure Registry, a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to ruxolitinib during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes,

including effects on postnatal growth and development, will be assessed through at least the first year of life. For more information, see the May 2019 FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies.[30]

2. The applicant should be required to conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to ruxolitinib during pregnancy compared to an unexposed control population.
3. The applicant should be required to conduct a lactation study (milk only) in women prescribed ruxolitinib who are willing to discontinue breastfeeding their infants. A milk-only study is recommended because of the risk of serious adverse events seen in adult patients who have taken ruxolitinib. In this type of study, the infant is not exposed to ruxolitinib. For more information, see the May 2019 FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design.[31]

[30] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safetystudies- guidance-industry

[31] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design

APPENDIX A

Applicant's Summary of Published Literature Regarding Ruxolitinib Use in Pregnant and Lactating Women and Effects on Fertility[32]

Author (Year)	Title	Type of Study (Study Design)	Number Exposed/Unexposed	Endpoints and Outcomes of Study
Gerds and Dao 2017	Polycythemia Vera Management and Challenges in the Community Health Setting.	N/A	N/A	Ruxolitinib was described as a traditional treatment option for PV and separately discussed pregnancy in PV patients as a special consideration for community-based hematologists. As disease onset is usually later in life, pregnancy is relatively rare in patients with PV and comes with increased risk. Ruxolitinib has not been evaluated in pregnant patients who have PV and should be avoided.
Comment: The USPI states that there are no studies with the use of Jakafi in pregnant women to inform drug-associated risks which is consistent with the author's assessment.				
Kong et al 2017	The potential impact on future fertility for biologics and emerging therapies for psoriasis and atopic dermatitis.	Retrospective review of FDA, European Union (EU), and Health Canada regulatory data, as well as medical literature.	N/A	The effect of new biologics and systemic medications for treatment of psoriasis and atopic dermatitis on fertility is largely unknown, however, available data suggests that most of the treatments have no adverse effects. For females, 27% (3/11) of medications represented a potential fertility risk in animal studies without human data (Category C-ruxolitinib). In animal studies, for males, 82% (9/11) of medications did not show toxicity to sperm. (Category B-ruxolitinib). The limited data, underscores the need for longer outcome tracking and the further assessment of fertility.
Comment: The USPI for oral ruxolitinib states that there were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). The impact of emerging therapies for psoriasis and atopic dermatitis on future fertility remains an area that requires further surveillance and assessment.				

[32] Applicant's table, copied from May 17, 2021 IR response for NDA 215309

Author (Year)	Title	Type of Study (Study Design)	Number Exposed/Unexposed	Endpoints and Outcomes of Study
Barzilai et al 2017	Characteristics and Outcome of Philadelphia (Ph) Negative Myeloproliferative Neoplasms (MPN) in Patients Younger than 45 Years – a Multicenter Retrospective Study.	A retrospective study.	10% were treated with a cyto-reductive therapy (interferon, anagrelide, ruxolitinib)	This retrospective study included 106 patients 18-45 years of age at the time of diagnosis of Ph-negative MPN, between 1985-2017. At diagnosis, 35% were treated with hydroxyurea, 10% with another cyto-reductive therapy (interferon, anagrelide, ruxolitinib) and 55% did not receive any cyto-reductive therapy. After diagnosis of MPN, 25 women became pregnant (46 pregnancies). Pregnancy outcomes: 4 spontaneous abortions, 2 fetal malformation, and 1 premature delivery (the article did not specify if any of the 25 pregnant women were exposed to ruxolitinib).
Comment: This article highlights the challenges younger patients with a diagnosis of MPN face, such as long-term side effects, fertility issues and prevention of disease progression. Based on the aggregate data provided in this published literature article, it is not possible to determine if any of the 25 pregnant women were exposed to ruxolitinib during their pregnancy.				
Ianotto et al 2018	Myeloproliferative neoplasms in patients below 25 years old at diagnosis: A single centre experience.	Retrospective analysis of young patients with MPN diagnosed or followed by the author's department.	3	To improve knowledge of young patients with MPN, a cohort of 57 patients aged <25 years at the time of MPN diagnosis, were analysed. They were mostly females (34-58.6%) with median age of 19.7 years at diagnosis. All patients received a least 1 treatment for the MPN – including antithrombotic drugs (80.7%), phlebotomy in 84.6% of PV cases and cytoreductive drugs in 59.6%. Ruxolitinib was prescribed in 3 (8.6%). Thirty-nine pregnancies occurred in 13 women (the article did not specify if any of these 13 pregnant women were exposed to ruxolitinib), 24 (61.5%) babies born alive, 2 are ongoing and 11 were medically terminated or were miscarriages (as reported in article).
Comment: This article highlights the limited guidance that exists for MPN patients aged less than 25 years and the need for careful follow-up and treatment in this patient population. Based on the aggregate data provided in this published literature article, it is not possible to determine if any of the 13 pregnant women were exposed to ruxolitinib during their pregnancy.				

Author (Year)	Title	Type of Study (Study Design)	Number Exposed/Unexposed	Endpoints and Outcomes of Study
Yakuwa and Nakajima 2018	Congenital Anomalies.	N/A	N/A	There is a possibility that administration of JAK inhibitors (tofacitinib, baricitinib, ruxolitinib) during pregnancy may increase since rheumatoid arthritis and inflammatory bowel disease are prevalent in women of childbearing age. No teratogenic effects have been identified in reproduction studies with ruxolitinib. In the package insert in Japan, these drugs are contraindicated in pregnancy.
Comment: The USPI for oral ruxolitinib states that there are no studies with the use of Jakafi in pregnant women to inform drug-associated risks. The background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk in the U.S. general population of major birth defects is 2% to 4% and miscarriage is 15% to 20% of clinically recognized pregnancies.				
Wang and Wang (2019)	Multicenter study of ruxolitinib combined DEP regimen as a salvage therapy for refractory/relapsed hemophagocytic lymphohistiocytosis.	Prospective study aimed to investigate the efficacy of ruxolitinib combined with previous DEP (doxorubicin-etoposide-methylprednisolone) regimen (DEP-Ru) as a salvage therapy for refractory/relapsed(R/R) hemophagocytic lymphohistiocytosis (HLH).	54 R/R HLH patients enrolled.	Compared with DEP regimen, DEP-Ru regimen had similar efficacy and no serious complications. DEP-Ru regimen is an effective salvage regimen for R/R HLH, which can prolong patient survival. The article mentioned only 1case of pregnancy. No other details regarding the pregnancy or pregnancy outcome were provided.
Comment: The limited information in the literature article regarding the 1 case of pregnancy precludes any medical assessment.				
Wang et al 2020	Etoposide combined with ruxolitinib for refractory hemophagocytic lymphohistiocytosis during pregnancy: a case report	Case report	1	This is the first case report of etoposide combined with ruxolitinib in the treatment of patients with refractory secondary Hemophagocytic lymphohistiocytosis (HLH) during pregnancy.

Comment: This case report is captured in the global safety database under case ID (b) (6) and is included in the analysis of pregnancy reports in response to Question 2 below for oral ruxolitinib. The pregnancy outcome in this case was induced abortion.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JEAN L LIMPERT
05/21/2021 05:49:19 PM

MIRIAM C DINATALE
05/21/2021 06:00:59 PM

LYNNE P YAO
05/24/2021 09:02:28 AM

Clinical Inspection Summary

Date	5/21/2021
From	Phuc Nguyen M.D., Medical Officer Karen Bleich, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief/Acting Division Director Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Brenda Carr M.D., Medical Officer Snezana Trajkovic, M.D., Team Leader Kendall Marcus, M.D., Division Director Division of Dermatology and Dentistry
NDA	215309
Applicant	Incyte Corporation
Drug	Ruxolitinib cream
NME	No
Therapeutic Classification	Multikinase Inhibitor - Immunomodulator
Proposed Indication	Atopic dermatitis
Consultation Request Date	1/28/2021
Summary Goal Date	5/21/2021
Action Goal Date	6/21/2021
PDUFA Date	6/21/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies INCB 18424-303 and INCB 18424-304 were submitted to the Agency in support of a New Drug Application (NDA 21509) for ruxolitinib cream for the above proposed indication. Four clinical investigators (Dr. Robert Call, Dr. Joseph Lillo, Dr. Amit Patel, and Dr. Julie Shepard) were selected for clinical inspection.

The inspections revealed findings that are unlikely to have a significant impact on overall trial safety or efficacy results. There were unreported AEs, including one instance of low hemoglobin (grade 2) that resolved. These AEs, as noted below, are unlikely to significantly affect overall reliability of safety and efficacy data or change proposed labeling. Based on these inspections, Studies INCB 18424-303 and INCB 18424-304 appear to have been adequately conducted and the study data generated appear acceptable in support of the respective indication in the NDA.

II. BACKGROUND

Incyte Corporation has submitted a new drug application, under a Rare Pediatric Disease Priority Review Voucher (PRV), for ruxolitinib cream, a previously approved molecular entity, as a topical treatment for atopic dermatitis in adolescents and adults. Ruxolitinib is a Janus kinase (JAK) 1/2 inhibitor, a selective immunomodulator drug. The topical formulation, ruxolitinib cream, is under investigation for treatment of inflammatory skin conditions, including atopic dermatitis.

Atopic dermatitis is a chronic, recurring, inflammatory, and pruritic skin condition that affects worldwide up to 25% of children and up to 12% of adults according to the sponsor. The submitted phase 3 clinical trials data supporting the safety and efficacy of ruxolitinib cream to treat atopic dermatitis in adults and adolescents 12 years of age or older come from two identical studies (INCB 18424-303, INCB 18424-304). Inspections were requested for both studies.

Study INCB 18424-303
Title of Study: *A Phase 3, Double-Blind, Randomized, 8-Week, Vehicle-Controlled Efficacy and Safety Study of Ruxolitinib Cream Followed by a Long-Term Safety Extension Period in Adolescents and Adults With Atopic Dermatitis*

Per the protocol, this was designed to be a domestic and international, multicenter, phase III, placebo-controlled, double blind, randomized study. Eligible subjects were adolescents and adults, males and non-pregnant females aged 12 years or older (note: participants in Canada were 18 years or older) with a preexisting diagnosis of atopic dermatitis of at least 2 years, a baseline Investigator Global Assessment (IGA) score of 2 to 3, and a % body surface area (BSA) involvement of 3-20%, excluding scalp involvement, at the time of screening.

Patients were to be randomized to study treatment arms in a 2:2:1 ratio to ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID, or vehicle (placebo) cream BID, in a blinded manner for the 8 weeks in the vehicle control (VC) period, followed by a 44-week double-blind long-term safety (LTS) period. During the LTS portion of the trial, all subjects were to receive active treatment. Subjects who had been on active treatment in the VC period were to continue their treatment. Subjects who had been on vehicle cream were to be randomized to one of the two active treatment doses. Duration of treatment for an individual participant is approximately 60 weeks (28 days for screening, 8 weeks in the VC period, 44 weeks in the LTS period, and 30 [+ 7] days of safety follow-up).

Incyte Corporation lists itself as the monitor to ensure subject safety (safety reporting and assessments during the trial). Data was to be collected via a provided eCRF system.

The primary efficacy endpoint for the study was defined as the proportion of patients achieving Investigator's Global Assessment – Treatment Success (IGA-TS) at Week 8 score of 0 or 1 with a ≥ 2-grade improvement from baseline.

Per the study report, the study was conducted at 78 sites in North America and Europe, with the majority being US sites. The study period began on December 20, 2018, and the data cut-off date was June 22, 2020. A total of 631 participants were randomized into this study.

Study INCB 18424-304
Title of study: *A Phase 3, Double-Blind, Randomized, 8-Week, Vehicle-Controlled Efficacy and Safety Study of Ruxolitinib Cream Followed by a Long-Term Safety Extension Period in Adolescents and Adults With Atopic Dermatitis*

The study protocol was identical to Study INCB 18424-304. Per the study report, the study was conducted at 65 sites in North America and Europe, with the majority being US sites. The study period began on December 20, 2018, and the data cut-off date was June 22, 2020. A total of 618 participants were randomized into the study.

III. RESULTS (by Site)

1. Call, Robert M.D.
   7110 Forest Avenue, Suite #201, Richmond, VA 23226
   Study: INCB18424-304
   Site: 416
   Dates of inspection: 3/22/2021-3/25/2021

At the time of the inspection, there were 69 subjects screened and 45 subjects randomized into the study. 45 subject records were reviewed.

The source records for the primary endpoint, IGA-TS ratings, were reviewed for 19 of the enrolled subjects and compared with the submitted subject data line listings. No data discrepancies were identified. The inspection revealed no deficiencies with maintenance of the blind. There was one unreported adverse event: Subject (b) (6) (vehicle cream/ ruxolitinib 1.5%) had a 'cold' classified as grade 1 from (b) (6).

Two unreported protocol deviations were identified. Subject (b) (6) (ruxolitinib 1.5%) did not have serum chemistry and hematology lab assessments at the week-8 visit. Subject (b) (6) (ruxolitinib 0.75%) did not receive a comprehensive physical exam during the week-8 visit.

Three unreported concomitant medications were identified. Subject (b) (6) 1 (vehicle cream/ruxolitinib 1.5%) was taking losartan 50 mg beginning in (b) (6) with unknown duration, and metoprolol ER 50 mg starting (b) (6) with unknown duration. Subject (b) (6) (vehicle cream/ruxolitinib 1.5%) was taking Theraflu 20 mg starting (b) (6) with unknown duration.

The original screening ECG chart for Subject (b) (6) (ruxolitinib 0.75%) was missing from the subject records. Clinical site staff did note that an ECG was performed during that visit.

Reviewer comment: The unreported adverse event, protocol deviations, concomitant medications, and the missing ECG do not appear to be clinically significant. Based on the nature of the violations it is unlikely they significantly affect overall reliability of the safety and efficacy data generated from the site. There is no evidence of subject harm related to the described findings. The inspection findings were acknowledged by Dr. Call during the inspection and he stated that he would implement a checklist program to prevent further mistakes.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for regulatory violations related to the described findings.

2. Lillo, Joseph
   4520 East Indian School Road, Suite #1, Phoenix, AZ 85018
   Study: INCB18424-303
   Site Number: 327
   Dates of inspection: March 15-19 and 22, 2021

There were 35 subjects screened and 28 subjects randomized into the study. All 35 subject records were reviewed.

There were no issues with the adequacy of source documentation. The source records of IGA scores at baseline and week 8 were reviewed for all enrolled subjects. No discrepancies were identified in the primary endpoint data in the source records and the information reported in the subject data line listings. The inspection revealed no deficiencies with the maintenance of the blind.

Some IGA scores in the source records were not included in the data listings from prior to the cutoff date. They are listed in Table 1 below.

Table 1: IGA scores not reported to the sponsor, before the data cut-off date: June 22nd, 2020

Subject # (Treatment Assignment)	Week: IGA Score	Date	Notes
(b) (6) (ruxolitinib 1.5%)	Week 40: 0 Week 44: 2 Week 48: 1	(b) (6)	Telephone visits due to COVID19
(b) (6) (ruxolitinib 0.75%)	Week 36: 1 Week 40: 2		Telephone visits due to COVID19
(b) (6) (ruxolitinib 0.75%)	Week 28: 0		Telephone visit due to COVID19

Reviewer's Comment: Although the above should have been reported to the sponsor as they pertain to data before the data cut-off date, these IGA scores fall outside the time period used to evaluate primary efficacy endpoint per the protocol. These data points are unlikely to significantly affect overall reliability of safety and efficacy data from the site.

There were 5 adverse events that were not reported to the sponsor, as captured in the table below:

Table 2: Adverse events that were not reported to the sponsor

Subject # (Treatment Assignment)	Adverse Event	Start/End Date	Grade
(b) (6) (ruxolitinib 0.75%)	Umbilical Hernia	(b) (6)	2
(b) (6) (ruxolitinib 0.75%)	Laceration (right) lower leg		2
(b) (6) (ruxolitinib 1.5%)	Elective cataract surgery O.D.		1
(b) (6) (ruxolitinib 1.5%)	Low hemoglobin		2
(b) (6) (ruxolitinib 0.75%)	Viral URI		2

Reviewer comment: Although the above adverse events should have been reported to the sponsor, they appear unlikely to significantly affect overall reliability of safety and efficacy data from the site. Anemia/low hemoglobin is already a component of the warnings and precautions portions of proposed product labeling.

An unreported protocol deviation regarding eligibility criteria was identified. Subject (b) (6) (ruxolitinib 0.75% arm) had an ALT value of 82 U/L (reference range 10-40) on the screening serum chemistry, meeting eligibility criteria #8 (AST or ALT ≥2 x ULN). The subject consented to the trial and underwent screening procedures on (b) (6), including serum chemistry. On (b) (6) (baseline visit) Subject (b) (6) was enrolled into the trial and randomized to the ruxolitinib 0.75% arm. The subject was subsequently discontinued from the study on (b) (6) after attempts to contact him after (b) (6) were unsuccessful.

Reviewer comment: Subject (b) (6) met an exclusion criterion regarding abnormal liver enzymes and should not have been enrolled in the study. Additionally, Dr. Lillo failed to report the protocol deviation to the sponsor or to the IRB. The ALT value decreased to 67 U/L on the serum chemistry dated (b) (6) (reported on (b) (6)) suggesting that there was unlikely to have been harm to the subject related to the protocol deviation. The investigator failed to reach the subject by phone and by certified mail.

Dr. Lillo was given an opportunity to explain and present a corrective and preventative action plan on the observations above. No written response has been received.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for regulatory violations related to the described findings. Although a Form FDA-483 was issued for regulatory violations, based on the nature of the violations, they are unlikely to significantly affect overall reliability of safety and efficacy data from the site.

3. Patel, Amit
   4646 Brockton Avenue, Suite #205, Riverside, CA 92506
   Study: INCB18424-303
   Site Number: 301
   Dates of inspection: March 8 to 11, 2021

There were 19 subjects screened and 13 subjects randomized into the study. 13 subject records were reviewed.

There were no issues with the adequacy of source documentation. The inspection found no deficiencies with the maintenance of the blind. The subject data line listings for IGA score and EASI score were verified with source documents for all randomized subjects.

Two unreported adverse events were identified. Subject (b) (6) (ruxolitinib 1.5%) was enrolled on (b) (6) and reported increased sciatica pain on (b) (6). The source record does not include a start or end date nor a severity grade for the event. There is no entry for sciatica pain at any time in the sponsor's data listing for Subject (b) (6) Subject (b) (6) (ruxolitinib 1.5%) was enrolled on (b) (6) and reported ongoing abdominal pain on (b) (6) No start date, end date, or severity grade is reported in the source record. There is no entry for abdominal pain at any time in the sponsor's data listing for Subject (b) (6)

Reviewer comment: The unreported adverse events (sciatica pain and abdominal pain) should have been reported and fully documented including severity grade. Although the above adverse events should have been reported to the sponsor, based on the nature of the adverse events that they appear unlikely to significantly affect overall reliability of safety and efficacy data from the site.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. Form FDA-483 was not issued.

4. Shepard, Julie
   7200 Poe Avenue, Suite #200, Dayton, OH 45414
   Study: INCB18424-304
   Site Number: 435
   Study: INCB 1824-303
   Site Number: 206
   Dates of inspection: March 9-18, 2021

For Study INCB 18424-304, there were 47 subjects screened and 20 subjects randomized into study INCB 1824-304. For Study INCB 18424-303, there were 4 subjects screened and 3 subjects randomized into study INCB 1824-303. Source records were reviewed for all

subjects participating in the two studies at the site, including verification of the primary endpoint data provided in the data listings for IGA and EASI. There were no discrepancies.

Minor protocol deviations were noted. Two subjects' ECG were not original copies; subject identifiers were added to the ECGs after the documents were copied, and it is unclear who added this information, and thus we cannot be sure it was done correctly. The list of subjects and dates are below.

- Subject (b) (6) (ruxolitinib 1.5%)—ECG date: (b) (6)
- Subject (b) (6) (vehicle cream/ruxolitinib 0.75%)—ECG date: (b) (6)

A few of the fail-screened subject's records had cross-outs and inadequate capture of the reasoning for failed screenings. Also, at the time of the inspection visit—at which time the study is no longer active—access to the investigational drug storage cabinet did not have adequate record keeping of by whom, and when they were accessed.

Reviewer comment: *It is unlikely that the annotation issues and drug cabinet log issue described above significantly impacted trial safety or efficacy data, or to have caused subjects harm. Dr. Shepard, in her written response, documents plans for preventative actions, including ensuring adequate documentation on original documents, improving annotations for patients meeting inclusion and exclusion criteria in future studies, and improving protocol for documenting drug cabinet access.*

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. No Form FDA-483 was issued. The findings above are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable in support of the NDA.

{See appended electronic signature page}

Phuc Nguyen, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief/Acting Division Director
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm./ NDA 215309
DDD/Division Director/ Kendall Marcus
DDD /Team Lead / Snezana Trajkovic
DDD /Clinical Reviewer/ Brenda Carr
DDD /Regulatory Project Manager/ Matthew White
OSI/DCCE/Acting Division Director/ Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Karen Bleich
OSI/DCCE/GCPAB Reviewer/Phuc (Phil) Nguyen
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHUC L NGUYEN
05/20/2021 09:57:41 AM

KAREN B BLEICH
05/20/2021 10:10:42 AM

KASSA AYALEW
05/20/2021 10:34:33 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 30, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 215309
Product Name, Dosage Form, and Strength:	ruxolitinib cream, 1.5%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Incyte Corporation
FDA Received Date:	December 21, 2020
OSE RCM #:	2020-2688
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for ruxolitinib cream, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed ruxolitinib prescribing information (PI), patient package insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Patient Package Insert (PPI), interim container labels, container labels, and carton labeling. We note the applicant has proposed interim container labels to be used until pre-printed empty aluminum tubes are available. We also note the use of the proposed proprietary name, (b) (4) *** which we found unacceptable due to similarity in pronunciation with another product[a]. We find all the labels and labeling can be improved by using the placeholder "TRADENAME" until a new name is found to be conditionally acceptable. Additionally, the labels and labeling can be improved to prevent wrong strength and deteriorated drug errors and to facilitate product identification. The carton

[a] Patel, M. Proprietary Name Review for (b) (4) *** (NDA 215309). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 22. PNR ID. 2020-1044462714.

labeling can also be improved to align formatting of product identifiers with the FDA released draft guidance on product identifiers[b].

4 CONCLUSION & RECOMMENDATIONS

We find all labels and labeling can be improved by using the placeholder "TRADENAME" until a new name is found to be conditionally acceptable. Additionally, the labels and labeling can be improved to prevent wrong strength and deteriorated drug errors and to facilitate product identification

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. Prescribing Information

1. General Comments
    a. The proposed proprietary name, (b) (4) ***, used throughout the prescribing information (PI) and Patient Packaging Insert (PPI) was found unacceptable by DMEPA under NDA 215309 on March 22, 2021 due to similarity in pronunciation with another product. Remove the proposed proprietary name, (b) (4) ***, throughout the PI and PPI. Until a new name is found to be conditionally acceptable, the placeholder, "TRADENAME" may be used.

4.2 RECOMMENDATIONS FOR INCYTE CORPORATION

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The proposed proprietary name, (b) (4) ***, used throughout the container label and carton labeling, was found unacceptable by DMEPA under NDA 215309 on March 22, 2021 due to similarity in pronunciation with another product. Remove the proposed proprietary name, (b) (4) ***, throughout the container labels and carton labeling. Until a new name is found to be conditionally acceptable, the placeholder, "TRADENAME" may be used. Once a proprietary name is found conditionally acceptable, the placeholder "Tradename" must be replaced with the proprietary name on the container labels and carton labeling and the revised labels and labeling must be submitted to the Agency for review.
2. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

[b] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

3. To ensure consistency with the Prescribing Information, revise the [redacted] statements to read either "Recommended Dosage: Apply twice daily to the affected areas. See prescribing information." or "Recommended Dosage: See prescribing information."

3 Page(s) of Draft Labeling

B. Container Labels

1. We note the pre-filled tubes with the interim labels, will have the expiration date on the tube crimp. However, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date

2. Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to tube curvature.[c]

C. Carton Labeling

1. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[d] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode.

NDC: [insert product's NDC]
SERIAL: [insert product's serial number]
LOT: [insert product's lot number]
EXP: [insert product's expiration date]

[c] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

[d] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for ruxolitinib received on December 21, 2020 from Incyte Corporation.

Table 2. Relevant Product Information for ruxolitinib	
Initial Approval Date	N/A
Active Ingredient	ruxolitinib
Indication	topical treatment of atopic dermatitis in patients 12 years of age and older
Route of Administration	topical
Dosage Form	cream
Strength	1.5%
Dose and Frequency	Apply a thin layer twice daily to affected areas up to 20% of body surface area
How Supplied	60 g tube, 5 g (professional sample)
Storage	room temperature 68°F to 77°F (20°C to 25°C); excursions within 59°F to 86°F (15°C to 30°C) are permitted
Container Closure	aluminum tubes

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following ruxolitinib labels and labeling submitted by Incyte Corporation.

- Container Labels received on December 21, 2020
- Carton Labeling received on December 21, 2020
- Professional Sample Container Labels received on December 21, 2020
- Professional Sample Carton Labeling received on December 21, 2020
- Prescribing Information (Image not shown) received on December 21, 2020, available from \\CDSESUB1\evsprod\nda215309\0001\m1\us\draft-labeling-text.pdf
- Patient Package Insert (Image not shown) received on December 21, 2020, available from \\CDSESUB1\evsprod\nda215309\0001\m1\us\draft-patient-info-text.pdf

G.2 Label and Labeling Images

(b) (4)

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
03/30/2021 10:17:07 AM

SEVAN H KOLEJIAN
03/30/2021 12:09:58 PM